invention at the time of filing. *See* Vas-Cath v. Mahurkar, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). The Patent Office notes (at page 3 of Paper No. 8) that "possession" can be shown through a variety of ways. In looking at the issue of possession, both the Patent Office Guidelines (66 FR 1099 (Jan. 5, 2001) ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, 'Written Description' Requirement") and the relevant cases from the Federal Circuit indicate that at least the following factors should be considered: 1) the level of skill and knowledge in the art; 2) disclosure of a partial structure; 3) disclosure of physical and/or chemical properties; 4) disclosure of functional characteristics; and 5) the method of making the claimed invention.

A review of these factors clearly shows that applicants have sufficiently described the claimed subject matter in this case. First, applicants describe the complete sequence of calpastatin in, for example, SEQ ID NO: 1. Any fragment of calpastatin can be derived from the structural information in that sequence listing. Thus, one skilled in the art would know that any partial structure, or fragment, can be derived from this sequence. One would need no further information to derive a deletion, substitution, or fragment.

As an example, applicants specifically describe a fragment of calpastatin in SEQ ID NO:3 or 4 (originally SEQ ID NO: 2, but amended by the Preliminary Amendment of September 24, 1999), which also possesses the ability to specifically or preferentially inhibit the degradation of wild-type p53 by calpain (*see* page 7, lines 13-20). Comparing the sequences 1 and 2 of the original sequence listing filed with the application, one can easily determine that the fragment of SEQ ID NO: 2 is an internal fragment from amino acid 137 to 269 of SEQ ID NO:1. Since this fragment is bordered by trypsin cleavage sites, Lys at 136 and Lys at 269, one skilled in the art would reasonably figure that this fragment corresponds to a trypsin-generated fragment. Here, enzymatic cleavage represents a non-functional way of modifying calpastatin to test its activity relative to p53 degradation. Many other enzymes could also be selected in testing a fragment or part of calpastatin for its ability to inhibit calpain.

The fragment in the specification is both a C-terminal truncation and a N-terminal truncation. This would immediately mean to one skilled in the art that neither an N-terminal deletion nor a C-terminal deletion of calpastatin destroys the functional characteristics for the

purposes here. The sequences encoding the N-terminus and C-terminus are given. Therefore, one skilled in the art could have used the specific structural, sequence information of the specification, and the ability to substitute, delete, or change codons to derive any desired fragment or "part" of calpastatin. Furthermore, one could have used the examples in the specification to determine if the fragment is an inhibitor of calpain.

In addition, the knowledge of one skilled in the art included the consideration of numerous calpastatin proteins and fragments of them. The U.S. patent document 5,629,165 (Nixon *et* al., of record) discusses numerous calpastatins having differing molecular weights and N-terminal sequences, for example. That document also cites other reports that discuss the knowledge available concerning calpastatin proteins and fragments. This information could also be used to create nucleic acids encoding a calpastatin polypeptide or protein as discussed in the specification. Considering at least this additional knowledge of one skilled in the art, one would have reasonably recognized that applicants were in possession of the claimed invention.

Evaluating the disclosure under the proscribed rules of the PTO Guidelines, one skilled in the art would know that applicants possessed the subject matter claimed. There is no need for specific sequence information for every possible fragment or part of calpastatin. That type of disclosure requirement would not only be extremely cumbersome, but it also is not permitted by the PTO Guidelines or the cases underlying those Guidelines. Furthermore, this case clearly differs from situations where the full length sequence of a polypeptide, or cDNA, or polypeptide-encoding DNA is not known. Here, one of skill in the art is presented with and would have been aware of more than enough evidence that parts of calpastatin can be produced and used, indicating applicants were in possession of the invention claimed.

Applicants request reconsideration and withdrawal of this rejection.

2. Enablement

The previous rejection of claims 18-29 under 35 U.S.C. § 112, first paragraph, for scope of enablement has been withdrawn.

Claims 18-29 stand newly rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to contain a description of subject matter that enables one skilled in the art to make and/or use the invention claimed. Applicants respectfully disagree.

Applicants have described how calpastatin, fragments of calpastatin, and inhibitors of the activity of calpain can be used to regulate p53 levels (*see, for example,* Examples 2.2 and 3 at pages 22 and 23). One skilled in the art was familiar with mechanisms to address gene transfer into cells at the time the application was filed. One skilled in the art was also familiar with the p53 protein and methods for detecting its presence or activity in cells or samples from cells. Accordingly, in order to make and use the invention, one skilled in the art could have used any existing gene transfer method, any existing vector, and any existing assay of p53 levels. Everything else would be merely routine experimentation. Thus, applicants claimed invention has been enabled by the specification through the knowledge and skill of one of ordinary skill in the art.

The Patent Office asserts that undue experimentation would be required to practice the claimed invention (*see* pages 4-6 of Paper No. 8). As noted above, any experimentation would be merely routine. First, applicants have shown that fragments of calpastatin can be utilized to inhibit calpain (contrary to the statements at page 5 of Paper No. 8). The specification discloses a fragment and the knowledge of one skilled in the art at the time recognized that numerous fragments or sub-sequences of calpastatin, and other calpain inhibitors, could be selected or existed in nature. The cited documents Nixon *et al.* and Asada *et al.* also provide numerous examples of ways for selecting calpastatin fragments that could be used in conjunction with applicants' teachings. And at least Asada *et al.* EP 395 309 (of record) shows assays to test the ability to inhibit calpain (*see* col. 11, lines 53 through col. 12, line 15). It would only be routine to modify the DNA specifically recited in the specification to encode one of these or any other desired fragment or part of calpastatin and determine if it inhibits calpain.

It would also be routine for one skilled in the art to test a part of calpastatin, or fragment of calpastatin, or inhibitor of calpain activity, with a selected p53 mutant to determine if those p53 levels are regulated by calpain inhibition (contrary to the statements at page 5 of Paper No.

8). Example 1, 2, and 3 of the specification show how to assess the effect on p53, where any selected p53 mutant can be selected and used.

Thus, none of the concerns noted in Paper No. 8, pages 4-5, establish that the Patent Office has met is burden in showing that one of skill in the art would not believe that applicants have enabled their invention (*see* the Reply filed December 29, 2000, for a discussion of the appropriate standard, incorporated herein by reference).

The Patent Office also asserts that undue experimentation would be required to select an appropriate vector and route of administration that correlates with an effect on p53 in cells (*see* page 6 of Paper No. 8). Again, one of skill in the art had numerous vector systems from which to choose, numerous administration systems, and numerous methods for detecting p53 levels. It is not clear why selecting the appropriate vector for the desired cell type would be outside the skill in the art at the time the application was filed. That is, essentially, all that would be needed to make and use the invention claimed. Testing the p53 levels is also routine, no mater how many different p53 mutants or copies per cell apply to a desired application.

The Patent Office also discusses an unpredictability in achieving therapeutic levels of transgenes in a cell (*see* pages 6-8 of Paper No. 8). This reasoning cites a number of articles, which were previously addressed by applicants. These articles and the newly cited article address the clinical effectiveness, optimization of efficacy, and other clinical considerations for gene therapy. Applicants see that the Patent Office has not explicitly requested clinical trial data to support the claimed invention (as noted at pages 8-9 of Paper No. 8). But the repeated citation to articles that relate to the FDA standard and not the PTO standard at least implies that the only evidence sufficient to dispel the concerns of these articles is clinical trial evidence. That's the only type of evidence treated in these papers. Regardless, nothing in these papers says, or would be taken by one of skill in the art to say, that gene therapy is devoid of promising inventions or devoid of any patentable, pharmaceutical properties akin to those discussed in In re Brana (*see* applicants' Reply of December 29, 2000).

Applicants respectfully assert that, applying the appropriate standards, one of skill in the art would believe that applicants have enabled the claimed invention. This rejection should be withdrawn.

B. The Rejection Under 35 U.S.C. §112, Second Paragraph

The rejection of claims 18-28 under 35 U.S.C. § 112, second paragraph, has been withdrawn.

Claims 18-25 remain rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention. Applicants respectfully disagree.

The term "regulating," as the Patent Office pointed out at page 10 of Paper No.8, would be understood by one of skill in the art. However, applicants have amended claim 18 as suggested by the Examiner. Claim 18, and those dependent on it, now consistently refers to inhibiting calpain.

Applicants request reconsideration and withdrawal of this rejection.

C. The Rejection Under 35 U.S.C. § 102

The rejection of claims 26-29 under 35 U.S.C. § 102 over Nixon *et al.* has been withdrawn.

Claims 26, 28, and 29 now stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Asada *et al.* (J. Enz. Inhibit. 3:49-56 (1989)).

Applicants have amended claim 26 to recite a vector capable of transforming an animal cell. The Patent Office asserts that Asada "teaches a lambda phage viral vector" at page 11 of Paper No. 8. However, amended claim 26 recites a vector "capable of transforming an animal cell." Nothing in the Asada document demonstrates that any vector discussed within its four corners is capable of transforming an animal cell. Without a clear demonstration of this aspect of the amended claims and its dependent claims, Asada cannot anticipate claims 26, 28, or 29. *See* E.I. du Pont de Nemours v. Phillips Petroleum Co., 7 U.S.P.Q.2d 1129 (Fed. Cir. 1988).

Applicants respectfully request withdrawal of this rejection.

D. Conclusion

This application is now in condition for allowance. If the Examiner believes that prosecution might be furthered by discussing the application with applicant's representative, in person or by telephone, we would welcome the opportunity to do so.

Applicants have provided for a three-month extension above. No additional extension of time fees, requests for extension of time, petitions, or additional claim fees are believed to be necessary to enter and consider this paper or keep this application pending. If, however, any extensions of time are required or any fees are due in order to enter or consider this paper or enter or consider any paper accompanying this paper, including fees for net addition of claims, applicants hereby request any extensions or petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account # 50-1129 for any fees. If there is any variance between the fee submitted and any fee required, including the extension of time fee and fee for net addition of claims, the Commissioner is hereby authorized to charge or credit Deposit Account No. 50-1129.

Respectfully submitted,
Wiley Rein & Fielding LLP

Date: September 28, 2001

By: _____
David L. Kulik Reg. No. 36,576
Floyd B. Chapman Reg. No. 40,555

Wiley Rein & Fielding LLP
Intellectual Property Department
1776 K Street NW
Washington, D.C. 20006
Telephone: 202.719.7000
Facsimile: 202.719.7049

APPENDIX A
Marked-up version of rewritten claims 18 and 26, as required under 37 C.F.R. § 121

18. A method for [regulating cellular levels] inhibiting the degradation of p53 protein comprising administering to a cell[s] a vector comprising a nucleic acid encoding a protein or polypeptide, wherein the protein or polypeptide is an inhibitor of the activity of calpain, and wherein the encoded protein or polypeptide inhibits the activity of calpain upon its expression in the cell[s], thereby [regulating cellular] effecting the level[s] of p53 protein.

26. A viral vector comprising a nucleic acid encoding a protein or polypeptide, wherein the protein or polypeptide is an inhibitor of the activity of calpain, and wherein the vector is capable of transforming an animal cell.